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Randomized Control Trials

A double-blinded, randomized, parallel intervention to evaluate biomarker-based nutrition plans for weight loss: The PREVENTOMICS study

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SUMMARY

Background & aims: Growing evidence suggests that biomarker-guided dietary interventions can optimize response to treatment. In this study, we evaluated the efficacy of the PREVENTOMCIS platform—which uses metabolomic and genetic information to classify individuals into different 'metabolic clusters' and create personalized dietary plans—for improving health outcomes in subjects with overweight or obesity.

Methods: A 10-week parallel, double-blinded, randomized intervention was conducted in 100 adults (82 completers) aged 18–65 years, with body mass index ≥27 but <40 kg/m^2, who were allocated into either a personalized diet group (n = 49) or a control diet group (n = 51). About 60% of all food was provided free-of-charge. No specific instruction to restrict energy intake was given. The primary outcome was change in fat mass from baseline, evaluated by dual energy X-ray absorptiometry. Other endpoints included body weight, waist circumference, lipid profile, glucose homeostasis markers, inflammatory markers, blood pressure, physical activity, stress and eating behavior.

Results: There were significant main effects of time ($P < 0.01$), but no group main effects, or time-by-group interactions, for the change in fat mass (personalized: −2.1 [95% CI -2.9, −1.4] kg; control: −2.0 [95% CI -2.7, −1.3] kg) and body weight (personalized: −3.1 [95% CI -4.1, −2.1] kg; control: −3.3 [95% CI −4.2, −2.4] kg). The difference between groups in fat mass change was −0.1 kg (95% CI −1.2, 0.9 kg, $P = 0.77$). Both diets resulted in significant improvements in insulin resistance and lipid profile, but there were no significant differences between groups.

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Conclusion: Personalized dietary plans did not result in greater benefits over a generic, but generally healthy diet, in this 10-week clinical trial. Further studies are required to establish the soundness of different precision nutrition approaches, and translate this science into clinically relevant dietary advice to reduce the burden of obesity and its comorbidities.
Clinical trial registry: ClinicalTrials.gov registry (NCT04590989).

Abbreviations

BMI	body mass index
SNPs	Single-nucleotide polymorphism
DXA	dual-energy x-ray absorptiometry
HDL	high-density lipoprotein
LDL	low-density lipoprotein
oxLDL	oxidized low-density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
CRP	C-reactive protein
TNFα	tumor necrosis factor α
IL6	interleukin 6
IL10	interleukin 10
ICAM1	intercellular adhesion molecule 1
CD14	cluster of differentiation 14
MCP1	monocyte chemoattractant protein 1
ALT	Alanine aminotransferase
GGT	γ-glutamyltransferase
PUFA	polyunsaturated fatty acids
MUFA	monounsaturated fatty acids
MVPA	moderate-to-vigorous physical activity
CPM	counts per minute
PSS	perceived stress scale
TFEQ	three-factor eating questionnaire.

1. Introduction

Obesity, and particularly abdominal adiposity, is associated with various metabolic abnormalities [1]. Reduced high-density lipoprotein cholesterol (HDL-C) and increased concentrations of triglyceride and glucose, and elevated blood pressure, increase risk of type 2 diabetes, as well as cardiovascular morbidity and mortality [1]. According to the Global Burden of Disease study, obesity accounted for about 5 million deaths worldwide in 2019 [2]. Besides the physiological burden, healthcare costs attributable to overweight and obesity are considerable. On average, management of obesity accounts for 0.7–2.8% of national total healthcare expenditures [3] and, in Europe, approximately 7% of health care budget is spent on obesity-related diseases each year [4]. Early intervention via lifestyle modification may prevent the onset of obesity-related metabolic disorders, and may therefore reduce comorbidities and associated burden. However, despite considerable global efforts, obesity still represents one of the main public health challenges of modern era [2].

Diet has a vital role in preventing and managing obesity, but evidence from clinical studies demonstrates there is a great inter-individual variability in response to the same dietary intervention [5], which likely indicates that no one diet is superior to another [6–8]. Genetic variation as well as gut microbiome and environmental factors can influence how the body metabolizes, absorbs, and utilizes nutrients and other dietary components (as phytochemicals) [8–10]. Accordingly, tailoring nutrition recommendations according to genotypic and phenotypic characteristics of individuals could be more successful in achieving sustained changes in dietary behavior compared to population-based generic guidelines.

Over the past two decades, advances in "omics" technologies—genomics, metagenomics, transcriptomics, proteomics, and metabolomics—helped unravel the interactions between genes, gut microbiome and environmental factors at the molecular level [11]. Integrating these multi-omics offers unprecedented opportunities in multiple fields of science, including nutrition. In particular, the application of metabolomics in the nutrition sciences has deepened the understanding of the association between diet and health, and helped identify relevant biomarkers [11,12]. This has led to the emerging concept of "metabotyping" (metabolic phenotypes) which refers to stratifying individuals into relatively homogenous subgroups based on their similarities of metabolic signatures (i.e., metabolic profiling) [13]. Metabotyping represents a promising approach for delivering precision nutrition recommendations to optimize the benefits according to each subgroup's needs [9,14].

The H2020 PREVENTOMICS (Empowering consumers to PREVENT diet-related diseases through OMICS sciences) [15], coordinated by Eurecat in Spain, developed a platform with a Decision Support System tool that integrates genetic, nutritional, biochemical, physiological and behavioral factors and uses machine-learning techniques to classify individuals into different diet clusters. The platform aims to deliver personalized nutrition plans to ultimately drive sustainable healthy behavior change and thereby, prevent obesity-related diseases [15]. The objective of this 10-week randomized controlled trial (RCT) was to examine the efficacy of the PREVENTOMICS platform, incorporated in an e-commerce digital tool, for producing more favorable health outcomes over dietary plans based on general diet recommendations, in subjects with overweight or obesity and elevated waist circumference. We hypothesized that personalization of the diet would lead to greater body fat and weight loss, and greater improvements in cardiometabolic risk factors and inflammatory markers compared to a control, generic diet.

2. Methods

2.1. Study participants

Males and females aged 18–65 years with overweight or obesity, but otherwise healthy, were recruited through internet-based advertisements. Participants met inclusion criteria if they (a) had a body mass index (BMI) of ≥27 kg/m^2 but <40 kg/m^2; (b) elevated waist circumference (males >94 cm; females >80 cm); (c) smartphone; and (d) were able to provide an informed

consent. The exclusion criteria were as follows: (a) diagnosis of diabetes; (b) history or diagnosis of heart, liver or kidney diseases; (c) chronic diseases, e.g., cancer within the past 5 years (except adequately-treated localized basal cell skin cancer); (d) use of drugs (e.g., antibiotics) that, in the opinion of the medically responsible investigator, were likely to affect the primary outcomes of the study; (e) being lactating, pregnant or planning to become pregnant within the study period; (f) self-reported weight change of >5% within two months prior to screening; (g) participation in another clinical trial; (h) other blood donation during the study; (i) having allergies or food intolerances; and (j) having no or limited access to the internet. The study was registered at clinicaltrial.gov (NCT04590989) and approved by the Danish Ethical Committee (H-20029882). All study procedures were carried out in accordance with the Helsinki Declaration and the Danish Protection Agency, at the premises of the Department of Nutrition, Exercise and Sports (NEXS) at the University of Copenhagen during October 2020–June 2021. Written informed consent was obtained before the study start.

2.2. Study design and randomization

This was a 10-week randomized, single-center, parallel-group, double-blinded intervention study (Fig. 1). Participants were allocated in a 1:1 ratio, stratified by cluster (oxidative stress; inflammation; carbohydrate metabolism; lipid metabolism; microbiota-generated metabolites—see later for clustering process), to either the intervention group (personalized plan) or the control group (generic recommendations). Randomization was done by an independent statistician by using a computer-generated sequence with random permuted block sizes of two within each stratum [16].

Eligible subjects were invited for a pre-baseline visit where anthropometric measurements, blood, saliva, and urine samples were collected, and various questionnaires were filled out for cluster allocation and developing the personalized dietary plans for the subsequent 10-week intervention [16]. Primary and secondary endpoints were derived from measurements obtained before the start of the intervention (baseline) and at the end of the intervention.

All participants were classified by the PREVENTOMICS platform into one of five predefined 'clusters' based on (a) the subject's metabolome analysis of 51 biomarkers quantified in pre-baseline urine, plasma and serum samples (carried out by Eurecat, Spain); and (b) pre-baseline saliva analysis of 35 different single nucleotide polymorphisms (SNPs) which could affect the biomarker levels associated with the five clusters (carried out by Alimentomica, Spain). The specific SNPs together with the biomarkers provided a score for each cluster using proprietary algorithms for any given participant, considering both the absolute value of the biomarker in the biofluid and the biological relevance of the biomarker in the metabolic cluster. The former (absolute value) was directly obtained from blood and urine measurements (metabolomics biomarkers) and saliva (genotyping), whereas the latter (biological relevance) was obtained from different approaches combining artificial intelligence applied to measurements of different biobank samples and literature review [17]. The exact genetic and metabolomic biomarkers used in this study along with the rationale behind the scoring process have been described elsewhere [16]. The specifics of the algorithm cannot be disclosed due to a pending intellectual property rights application.

2.3. Interventions

2.3.1. Dietary intervention

The personalized plan and control groups received easy-to-prepare meal boxes twice a week from Simple Feast (Copenhagen, Denmark); the personalized and control diets were isocaloric and complied with national dietary guidelines on macronutrient distribution [18]. Each delivery provided meal boxes of breakfast and dinner for the subsequent three days (6 meals/delivery for a total of 12 meals/week). Meal boxes for the two groups were designed to be visually identical. Food by Simple Feast is vegetarian and organically produced, however, participants were allowed to eat non-organic/non-vegetarian food as part of the meals not provided (lunches and all Saturday meals). For these meals, they were encouraged to refer to recipes provided through the Simple Feast Recipe App, in order to prepare meals as similar as possible to the group and cluster they were assigned to. Additionally, they were instructed to consume the diets until they were fully satisfied. All provided foods and recipes were tailored by Simple Feast following the recommended list of food items to increase, decrease, or completely exclude from the diet, together with different functional ingredients (created specifically for each group and cluster by Eurecat's Nutrition Team); the calorie and nutrient content of the meals has been presented elsewhere [16]. Dietary adherence was assessed twice a week, through an electronic questionnaire, by

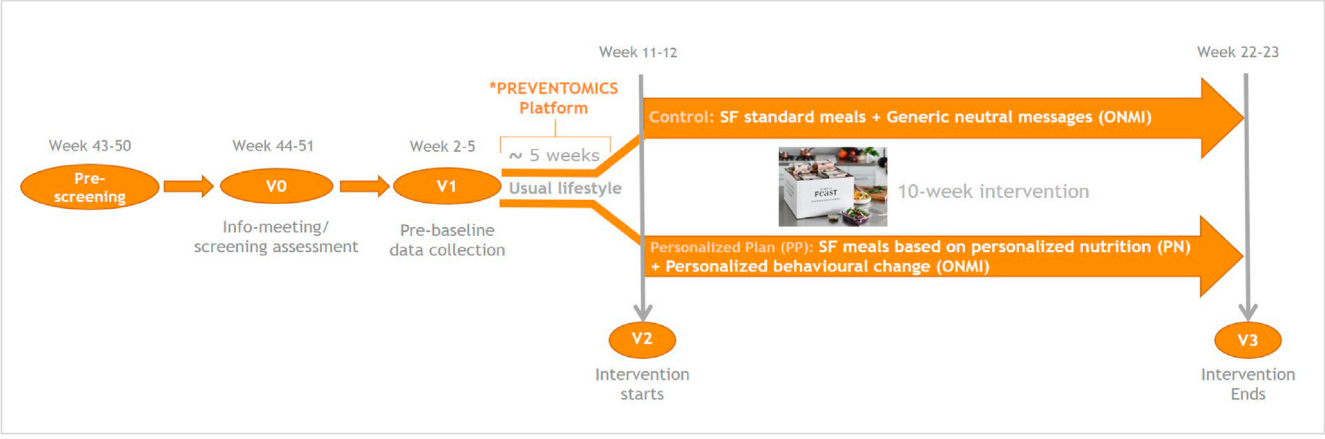

Fig. 1. Study design and timeline.*Approximately 5 weeks from the date of sending samples from the University of Copenhagen to the assigned partners (Eurecat, Alimentomica), to integrate results on subjects' metabolome and genotypes analysis into PREVENTOMICS platform. SF, Simple Feast.

reporting the proportion of food consumed from the meals provided by Simple Feast during the previous three days. A score from 1 to 3 was assigned to each meal, with higher scores indicating greater compliance, and the average was calculated.

2.3.2. Behavioral intervention

All participants were enrolled in a behavioral program delivered through ONMI's App (Behavior Change Technology, The Netherlands) with 2–3 electronic push notifications per week. Subjects randomized to the personalized group received behavioral prompts (active "Do") from the predefined ONMI's evidence-based behavioral change program, which has been developed to increase behavioral flexibility and facilitate adoption of healthier habits [19]. The "Do" prompts for the personalized group were based on subjects' individual behaviors (assessed by questionnaire at baseline) and inputs from Eurecat's Nutrition Team via the PREVENTOMICS platform, to provide a comprehensive behavioral change and improve adherence to the dietary intervention. In contrast, the messages for the control group were not personalized and were mostly informational in nature rather than prompting participants to take a specific action (i.e., general guidelines available from the National Health Service and the World Health Organization). The personalized and control groups received the same behavioral treatment in terms of volume (frequency and intensity) [16].

2.4. Assessments and outcomes

2.4.1. Anthropometrics and body composition

Body fat mass was determined before and after the 10-week intervention by use of dual-energy X-ray absorptiometry (iDXA, Lunar Radiation Co., Madison, Wisconsin, USA). Body weight was measured to the nearest 0.1 kg by using a calibrated digital scale (Tanita WB-110MA scale) with participants wearing light clothes and no footwear, after having voided. Height with no footwear was measured at screening to the nearest 0.5 cm using a wall-mounted stadiometer (Seca Telescopic Measuring Rod). Waist circumference (cm) was measured with a stretch-resistant tape at the midpoint between the lower margin of the last palpable ribs and the top of the iliac crest, in the fasted state while wearing light clothing and with an empty bladder. Each measurement was taken twice to the nearest 0.5 cm and the average was calculated.

2.4.2. Blood pressure and biochemical analyses

Resting blood pressure was measured by a calibrated automatic sphygmomanometer (A&D Instruments Ltd, Oxford, UK) and blood samples were collected from the antecubital vein after $\geq$10 h of fasting [16]. Blood for serum preparation was collected in serum clot activator tubes and stored at room temperature for approximately 30 min before centrifuging; blood for plasma preparation was collected in EDTA tubes and centrifuged immediately after collection. Conventional biochemical markers were measured at NEXS, University of Copenhagen. Plasma glucose and serum triglyceride, total cholesterol, low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively), C-reactive protein (CRP), uric acid, creatinine, γ-glutamyl transferase (GGT), and alanine aminotransferase (ALT) were measured by using commercially available assays on a Pentra 400 Analyzer (HORIBA ABX, France). Serum insulin was measured on the IMMULITE 2000 Immunoassay System (Siemens Healthcare Diagnostics Products Ltd, UK). Serum leptin and adiponectin, and plasma interleukins 6 and 10 (IL6 and IL10, respectively), tumor necrosis factor α (TNFα), monocyte chemoattractant protein 1 (MCP1), soluble intercellular adhesion molecule 1 (sICAM1), soluble cluster of differentiation 14 (CD14), and oxidized LDL (oxLDL) were determined by commercially available enzyme-linked immunosorbent assay kits. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting plasma glucose (mmol/L) × fasting plasma insulin (mU/mL)/22.5 [20].

2.4.3. Nutritional assessment

Participants completed 3-day estimated weight food records before and during week 3 of the 10-week intervention. The dietary records covered two non-consecutive weekdays and one weekend day. Nutrient analysis was carried out with Vitakost (Conava ApS; Kolding, Denmark), which is based on the Danish national food composition database (frida.fooddata.dk, version 4, 2019).

2.4.4. Eating behavior

Eating behavior was assessed by the three factor-eating questionnaire (TFEQ) [21]. This instrument is a 51-item self-reported questionnaire which measures three domains of eating behavior: (1) cognitive restraint of eating, (2) disinhibition, and (3) hunger. The minimum to maximum score is 0–21, 0–16 and 0–14 for restraint, disinhibition, and hunger, respectively. Higher scores indicate stronger characteristic values in the respective domain [21].

2.4.5. Stress assessment

Level of stress was measured through the 10-item perceived stress scale (PSS) [22]. The PSS is one of the most widely used psychological instruments, and measures the degree to which participants perceive events in their life as being stressful by asking about thoughts and feelings over the last month using a response scale from 0 (never) to 4 (very often).

2.4.6. Physical activity

Participants were asked to wear an ActiGraph tri-axial accelerometer monitor (ActiGraph LLC, Pensacola, FL, USA), secured with an adjustable elastic belt on the waist, for 7 consecutive days and 8 nights (i.e. 7 complete 24-h periods) before during week 3 of the 10-week intervention. They were only allowed to remove the monitor during water activities (i.e., showering or swimming). Raw accelerometer data were integrated into 60-sec epochs and analyzed using ActiLife version 6. Participants were instructed to keep logs for bedtime and waking time during the week in which the accelerometer was worn. Before analysis of physical activity, self-reported sleep duration was removed, together with non-wear time—defined as 60 min of consecutive zeros using vector magnitude, allowing for 2 min of non-zero interruptions with a maximum of 100 counts/min (CPM). Total physical activity (vector magnitude CPM) was expressed as vector magnitude of the total tri-axial counts divided by monitor wear time; in addition, daily step counts were recorded. Time (in minutes) spent in a sedentary state, doing light physical activity, and doing moderate-to-vigorous physical activity (MVPA) was defined as time with <200, 200–2689 and $\geq$ 2690 vector magnitude CPM, respectively [23]. The weekly averages of total physical activity, MVPA and step counts were calculated as weighted averages (averaging 5 weekdays plus 2 weekend days), and were only considered valid if monitor wear time was at least 8 h/day (excluding sleep duration) for a minimum of one weekday and one weekend day.

2.5. Power and statistical analyses

To detect a difference in body fat mass change of 1.25 kg between the personalized and control groups with 80% power at a two-tailed level of significance of 0.05, assuming a standard deviation (SD) of 2.0 kg, a sample size of 41 per group (personalized vs. control) was required, i.e., a total sample size of 82 completers. To allow for an anticipated 18% dropout rate, we planned to recruit 50 subjects per group (total n = 100). The expected difference in fat

mass between groups (1.25 kg) and the associated SD (2.0 kg) were based on values calculated from the raw data of the SHOPUS study [24] as detailed previously [16].

Data analysis was performed using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Differences in baseline characteristics of participants between the personalized and control groups were evaluated by using the independent t-test (or the Mann–Whitney U test in case of non-normally distributed data) for continuous variables and the Chi-square test for categorical variables, for purely descriptive purposes. Differences between groups in the primary outcome (fat mass change from baseline to end of trial) and all other outcomes were evaluated by linear mixed model (LMM) analysis that included random intercepts for participants, fixed effects for time (two levels: before vs. after the intervention) and diet group (two levels: personalized vs. control), and their interaction, with sex as covariate. An additional LMM analysis was performed in which cluster was also added as a fixed effect, to assess potential cluster-specific effects (main effects or interactions). The diagnostics considered for all models included verification of normality and homogeneity of variance by visual inspection of histograms and Q–Q plots, and plots of residuals against fitted values. Dependent variables with non-normally distributed residuals were log-transformed and expressed as percent change from baseline and percent difference between groups, with corresponding two-sided 95% confidence intervals (CI). The models were fitted using restricted maximum likelihood (REML) to accommodate data from participants with missing values at random in a single response variable [25]. Hence, LMM analyses were based on all 100 participants who started the intervention, unless otherwise stated. Data are shown as means with 95% CIs or SDs. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Study participants

From a total of 220 participants who responded to the advertisements, 106 were eligible for inclusion; 6 dropped out at the pre-baseline visit resulting in 100 participants completing the pre-baseline measurements and having their samples analyzed for metabolome and genotype before initiating the trial. The study flow chart is shown in Fig. 2. Participants were 21–65 years old (mean ± SD: 45 ± 11.5 years) with a BMI of 32 ± 3.5 kg/m^2 at the time of inclusion (Table 1). Of these, 82 participants completed the 10-week intervention resulting in a dropout rate of 18%. Reasons for dropping out included personal reasons, general health issues contraindicating continuation in the study (as judged by the study personnel or a medical expert), illness or acute infection, changes in medication not consistent with continuation, significant non-compliance with the study protocol or lack of cooperation, and lost to follow-up. Sixty nine percent of them were females, with equal sex distribution between the two arms (Table 1). There was a significant main effect for sex on body weight change, with females experiencing greater weight losses than males; hence all subsequent analyses were adjusted for sex.

3.2. Differences in primary and secondary outcomes

The difference in fat mass change between the personalized and control groups was −0.1 kg (95% CI -1.2, 0.9) ($P = 0.77$). In both groups, fat mass decreased over time ($P < 0.001$), by 2.1 kg (95% CI 1.4, 2.9) in the personalized group and by 2.0 kg (95% CI 1.3, 2.7) in the control group. The change in body weight ($P < 0.001$) followed the same pattern: personalized −3.1 kg (95% CI -4.1, −2.1) and control −3.3 kg (95% CI -4.2, 2.4). This modest weight and fat loss was accompanied by significant improvements in insulin resistance and lipid profile over time in both groups, with no significant time-by-group interactions or differences between groups (Table 2). All other outcome measures changed in a similar manner between the two diet groups with no significant differences between them (Table 2). There were also no significant 3-way interactions when cluster was also included in the analysis, suggesting the absence of cluster-specific differences between the personalized and control groups.

3.3. Dietary intake

No significant differences between groups were observed in dietary intake, except for fiber, which was greater in the personalized vs. control group (Table 2). Both groups reported consuming a similar amount of energy ($P = 0.92$), but both significantly reduced their protein intake relative to their habitual diets ($P < 0.001$). With regards to compliance, a Mann–Whitney U test indicated no significant difference ($P = 0.64$) among completers in dietary adherence score between the personalized diet group (median = 2.8, IQR 0.4) and the control diet group (median = 2.8, IQR 0.5).

3.4. Physical activity, eating behavior and stress

There were no significant differences between groups in total physical activity, MVPA and daily step count, even though arithmetically, physical activity increased in the personalized group and decreased in the control group (Table 2). No differences between groups were observed for changes in PSS and TFEQ (Table 2). Perceived stress did not change, whereas restraint eating significantly increased in both groups (all $P \leq 0.01$), and disinhibition ($P \leq 0.01$) and hunger tended to decrease ($P = 0.08$).

4. Discussion

While the emerging field of precision nutrition holds great promise in aiding health-related behavior change, inconclusive evidence so far exists to support such an approach in promoting weight and body fat loss. This 10-week trial demonstrated no additional benefit of personalizing dietary plans, over a generic approach, on the change in fat mass and body weight in individuals with overweight or obesity and elevated waist circumference. Accordingly, personalization of the diet did not significantly improve health parameters beyond the changes induced by the control diet. Participants in both groups lost approximately 3 kg of body weight. Although modest 5%–10% weight loss is generally recommended for improving health outcomes [26,27], the 3.2% weight loss in our study resulted in clinically relevant improvements in lipid profile and insulin sensitivity. For example, 53% out of 17 participants with prediabetes at baseline became normoglycemic after the intervention; 39% out of 39 who had insulin resistance (HOMA-IR ≥2) at baseline reduced their HOMA-IR to <2; and 48% out of 21 who had borderline high cholesterol concentrations (200–239 mg/dL) at baseline normalized (<200 mg/dL) after the intervention. Our results overall suggest that, against a background of a mostly plant-based and generally healthy diet, biomarker-driven personalization of the diet does not further improve body weight homeostasis, body composition, and cardiometabolic risk factors.

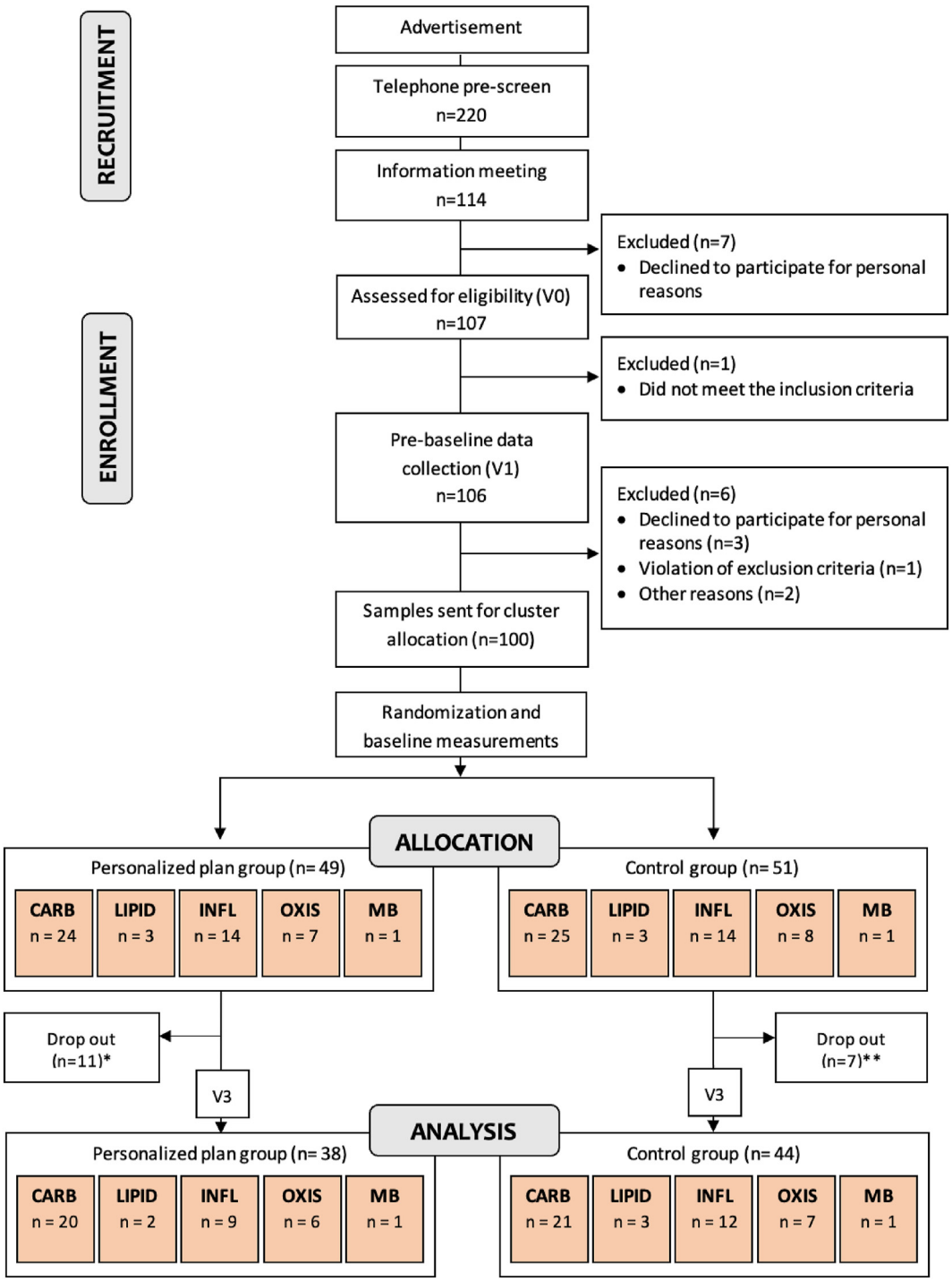

Fig. 2. Flow of subjects through the study. CARB, carbohydrate cluster; LIPID, lipid cluster; INFL, inflammation cluster; OXIS, oxidative stress cluster; MB, microbiota cluster. *Personal reasons (n = 3), non-adherence to diet (n = 3), illness or acute infection (n = 2), changes in medication (n = 2), lost to follow up (n = 1). **Personal reasons (n = 1), non-adherence to diet (n = 2), illness or acute infection (n = 1), serious adverse event (n = 1), pregnancy (n = 1), lost to follow up (n = 1).

4.1. Body weight and body composition

Our study is among the very few that used a double-blinded randomized design to prospectively assign participants to personalized or generic diet plans. Previously, the efficacy of metabotyping in weight management has been evaluated in observational studies and by post-hoc stratification of subjects in randomized trials, with substantial heterogeneity in their precision nutrition methodology, varying from using one or a few genetic or metabolic biomarkers to using complex machine-learning algorithms that include multiple parameters [13]. In the 12-month DIETFITS study, 609 adults with overweight were randomized to either a healthy low-fat diet or a healthy low-carbohydrate diet—both aiming at weight loss. The primary outcomes included change in weight but also the interaction between diet type with genotype and baseline insulin secretion, the latter two hypothesized as being biomarkers

Table 1
Baseline characteristics of subjects randomized in the personalized diet and control diet groups.

	Personalized n = 49	Control n = 51	*P*-value
Sex (% female)	37 (75%)	32 (63%)	0.17
Age (years)	45.5 ± 11.8	45.0 ± 11.4	0.84
Anthropometric measures			
Body weight, kg	94.3 ± 15.1	98.1 ± 16.2	0.24
Body mass index, kg/m^2	32.0 ± 3.6	32.3 ± 3.6	0.67
Waist circumference, cm	102 ± 11	103 ± 12	0.65
Lean body mass, kg	51.8 ± 9	55.7 ± 12	0.07
Fat mass, kg	39.2 ± 9.6	38.6 ± 9.2	0.77
Visceral adipose tissue, g	1291 (1036)	1398 (1423)	0.82
Total body fat, %	42 ± 6	40 ± 7	0.14
Vital Signs			
Systolic, mm Hg	123 ± 15	124 ± 20	0.86
Diastolic, mm Hg	86 ± 11	84 ± 10	0.28
Pulse, beats/min	66 ± 10	62 ± 10	0.03
Lipid profile			
Total cholesterol, mmol/L	4.9 ± 0.9	4.9 ± 0.8	0.99
HDL cholesterol, mmol/L	1.4 ± 0.3	1.4 ± 0.3	0.93
LDL cholesterol, mmol/L	3.0 ± 0.9	3.1 ± 0.7	0.65
Triglycerides, mmol/L	1.04 (0.8, 1.6)	0.93 (0.7, 1.3)	0.18
Glucose metabolism			
Glucose, mg/dL	94.3 ± 7.4	94.0 ± 10.3	0.85
Insulin, mU/L	6.8 (5.1, 10.5)	7.0 (4.2, 10.1)	0.43
HOMA-IR	1.6 (1.1, 2.6)	1.5 (1.0, 2.4)	0.45
Inflammatory markers			
oxLDL, mU/L	50,897 (42,308, 63,783)	47,973 (41,775, 55,701)	0.45
CRP, mg/L	1.8 (0.8, 3.4)	1.1 (0.7, 2.1)	0.05
TNFα, pg/mL	0.51 (0.42, 0.60)	0.44 (0.38, 0.56)	0.03
IL6, pg/mL	1.4 (1.0, 2.2)	1.1 (0.9, 1.9)	0.24
IL10, pg/mL	0.9 (0.4, 1.2)	1.1 (0.8, 1.5)	0.10
ICAM1, ng/mL	219 ± 39	200 ± 38	0.02
CD14, ng/mL	1359 ± 193	1257 ± 158	<0.01
MCP1, pg/mL	175 ± 33	179 ± 35	0.64
Adipokines			
Leptin, ng/mL	25.1 (17.0, 42.2)	21.3 (12.3, 35.4)	0.21
Adiponectin, μg/mL	6.1 (3.4, 7.6)	6.6 (4.0, 8.5)	0.35
Liver and renal biomarkers			
ALT, U/L	21 (14, 27)	20 (15, 29)	0.96
GGT, U/L	19 (16, 33)	22 (17, 35)	0.53
Creatinine, μmol/L	84.3 ± 10.9	87.4 ± 12.3	0.19
Uric acid, μmol/L	310 ± 74	309 ± 79	0.99
Dietary intake			
Energy, kcal/d	2196 ± 556	2456 ± 739	0.51
Fat, %E	37 ± 6	37 ± 8	0.76
Saturated fat, g/d	29.7 (23.0, 37.4)	32.6 (24.8, 44.1)	0.18
PUFA, g/d	9.6 (6.6, 12.0)	10.3 (6.6, 13.6)	0.53
MUFA, g/d	21.3 (15.6, 30.2)	22.3 (17.0, 33.2)	0.42
Protein, %E	16 ± 3	16 ± 4	0.90
Carbohydrate, %E	42 ± 8	42 ± 8	0.74
Dietary fiber, g/d	26 ± 9	25 ± 11	0.44
Added sugar, g/d	9.3 (1.4, 22.4)	10.9 (5.3, 32.0)	0.18
Physical activity level[a]			
MVPA, min/day	53 ± 28	56 ± 32	0.58
Total physical activity, CPM	593 ± 169	589 ± 171	0.91
Steps/day	7887 ± 2705	7873 ± 3285	0.98
Stress (PSS)	13.8 ± 7	13.5 ± 6	0.83
TFEQ			
Restrained eating	7.8 ± 4.2	7.5 ± 4.0	0.71
Disinhibition	10.3 ± 3.5	8.7 ± 3.3	0.02
Hunger	7.1 ± 3.5	6.6 ± 4.1	0.47

Data are presented as mean ± SD or median with quartiles, and comparisons between groups at baseline by using the t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Categorical variables were analyzed by Pearson's chi-square test. *P*-values are shown only for descriptive purposes and not for hypothesis testing.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; CRP, C-reactive protein; TNFα, tumor necrosis factor α; IL6, interleukin 6; IL10, interleukin 10; ICAM1, intercellular adhesion molecule 1; CD14, cluster of differentiation 14; MCP1, monocyte chemoattractant protein 1; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; MVPA, moderate-to-vigorous physical activity; CPM, counts per minute; PSS, perceived stress scale; TFEQ, three factor eating questionnaire.

[a] Personalized plan group (n = 49), control (n = 50).

for the success on each diet [28]. This study found no differences between groups in the changes in body weight, body fat percentage, and waist circumference, and no interactions with genotype or baseline insulin secretion [28]. Likewise, the NUGENOB, DiOGenes, and Food4Me studies also failed to observe significant gene–diet interaction effects on body weight responses to various diet treatments [29–31]. On the other hand, Hjorth et al. [32] reanalyzed data from 3 large weight-loss RCTs (DiOGenes, SHOPUS, and

Table 2
Changes in primary and secondary endpoints in the personalized diet and control diet groups.

	Personalized n = 49	Control n = 51	Mean difference (95% CI)	*P*-value
Anthropometric measures[a]				
Fat mass, kg	−2.1 ± 0.4[f]	−2.0 ± 0.3[f]	−0.1 (−1.2, 0.9)	0.77
Body weight, kg	−3.1 ± 0.5[f]	−3.3 ± 0.4[f]	0.2 (−1.2, 1.5)	0.77
Body mass index, kg/m^2	−1.05 ± 0.20[f]	−0.98 ± 0.20[f]	−0.07 (−0.52, 0.38)	0.76
Waist circumference, cm[b]	−2.1 ± 0.5[f]	−2.4 ± 0.5[f]	0.3 (−1.2, 1.8)	0.67
Lean body mass, kg	−0.8 ± 0.2[f]	−1.1 ± 0.2[f]	0.3 (−0.3, 0.9)	0.39
Visceral adipose tissue, g	−142 ± 38[f]	−152 ± 36[f]	10 (−95.0, 114.0)	0.86
Total body fat, %	−1.0 ± 0.2[f]	−0.9 ± 0.2[f]	−0.1 (−0.7, 0.5)	0.74
Vital signs[a]				
Systolic, mm Hg	−0.8 ± 2.4	0.4 ± 2.3	−1.1 (−7.7, 5.4)	0.73
Diastolic, mm Hg	−3.5 ± 1.1[f]	−2.7 ± 1.0[f]	−0.8 (−3.7, 2.1)	0.60
Pulse, beats/min	−3.0 ± 1.1[f]	−2.0 ± 1.1	−1.1 (−4.1, 2.0)	0.50
Lipid profile[a]				
Total cholesterol, mmol/L	−0.25 ± 0.10[f]	−0.28 ± 0.10[f]	0.03 (−0.20, 0.30)	0.81
HDL cholesterol, mmol/L	−0.07 ± 0.03[f]	−0.04 ± 0.02	−0.03 (−1.00, 0.04)	0.35
LDL cholesterol, mmol/L	−0.14 ± 0.07	−0.19 ± 0.07[f]	0.04 (−0.15, 0.24)	0.63
Triglycerides, mmol/L	−0.2 (−11, 11)	−0.5 (−10, 11)	0.1 (−14, 17)	0.99
Glucose metabolism[a]				
Glucose, mg/dL	−0.6 ± 0.9	−2.2 ± 0.9[g]	1.6 (−0.9, 4.1)	0.20
Insulin, mU/L	−12 (−22, −1)[g]	−12 (−21, −2)[g]	0.1 (−15, 18)	0.99
HOMA-IR	−13 (−23, −0.5)[g]	−14 (−24, −3)[g]	2 (−15, 21)	0.85
Inflammatory markers[a]				
oxLDL, mU/L	−2887 ± 1215[g]	−2670 ± 1133[g]	−216 (−3522, 3089)	0.90
CRP, mg/L	−1 (−23, 28)	−5 (−26, 20)	5 (−26, 49)	0.78
TNFα, pg/mL	0.02 ± 0.01	0.01 ± 0.01	0.01 (−0.03, 0.04)	0.70
IL6, pg/mL	−4 (−16, 11)	2 (−11, 16)	−5 (−22, 15)	0.58
IL10, pg/mL[c]	48 (21, 81)[f]	14 (−6, 37)	30 (−2, 71)	0.07
ICAM1, ng/mL	−7.0 ± 3.2[g]	−5.0 ± 3.0	−2.1 (−10.7, 6.5)	0.62
CD14, ng/mL	53 ± 25[g]	22 ± 23	31 (−37, 99)	0.37
MCP1, pg/mL	6.3 ± 3.3	1.7 ± 3.1	4.6 (−4.4, 13.6)	0.31
Adipokines[a]				
Leptin, ng/mL	−8.0 ± 1.3[f]	−5.7 ± 1.3[f]	−2.2 (−5.8, 1.5)	0.24
Adiponectin, μg/mL	0.10 ± 0.18	−0.21 ± 0.17	0.30 (−0.20, 0.80)	0.23
Liver and renal biomarkers[a]				
ALT, U/L	−1.7 ± 1.1	−2.4 ± 1.0[g]	0.7 (−2.3, 3.7)	0.66
GGT, U/L	1.0 ± 1.5	−2.8 ± 1.4[g]	3.9 (−0.3, 8.0)	0.07
Creatinine, μmol/L	−4.2 ± 1.5[f]	−3.8 ± 1.4[f]	−0.4 (−4.5, 3.9)	0.87
Uric acid, μmol/L	−5.2 ± 5.6	1.5 ± 5.2	−6.7 (−22.0, 8.5)	0.38
Dietary intake[d]				
Energy, kcal/day	−176 ± 101	−378 ± 96[f]	202 (−76, 479)	0.15
Fat, %E	−2.1 ± 1.2	−2.4 ± 1.1[g]	0.3 (−3, 3.6)	0.85
Saturated fat, g/d	−42 (−50, −32)[f]	−45 (−53, −37)[f]	6 (−14, 31)	0.60
PUFA, g/d	67 (41, 97)[f]	51 (28, 77)[f]	11 (−15, 28)	0.40
MUFA, g/d	−3 (−16, 13)	−7 (−19, 7)	5 (−16, 26)	0.67
Protein, %E	−1.9 ± 0.5[f]	−2.7 ± 0.5[f]	0.9 (−0.5, 2.2)	0.21
Carbohydrate, %E	3.6 ± 1.2[f]	5.0 ± 1.2[f]	−1.4 (−4.8, 2.0)	0.42
Dietary fiber, g/d	16.2 ± 2.0[f]	8.4 ± 1.9[f]	7.8 (2.4, 13.2)	<0.01
Added sugar, g/d	−48 (−67, −19)[g]	−54 (−70, −29)[f]	11 (−41, 108)	0.74
Physical activity level[e]				
MVPA, min/day	1.3 ± 4.0	−3.8 ± 4.0	5.1 (−6.0, 16.0)	0.35
Total physical activity, CPM	20 ± 24	−11 ± 23	32 (−35, 98)	0.35
Steps/day	504 ± 427	−167 ± 420	671 (−520, 1862)	0.26
Stress (PSS)[a]	−1.3 ± 1.0	−0.5 ± 1.0	−0.8 (−3.2, 1.5)	0.49
TFEQ[a]				
Restrained eating	1.5 ± 0.5[f]	1.1 ± 0.4[g]	0.5 (−0.8, 1.7)	0.47
Disinhibition	−1.0 ± 0.4[g]	−1.2 ± 0.4[f]	0.2 (−0.8, 1.2)	0.67
Hunger	−0.8 ± 0.5[g]	−0.8 ± 0.4	−0.0 (−1.3, 1.3)	0.96

Changes from baseline in each group are presented as means ± SEM based on estimates obtained from linear mixed models with participants as random effect; time, diet group, and their interaction as fixed effects; and sex as covariate. In case of non-normally distributed residuals, log-transformation was performed, and data thus represent mean percent change with 95% CI. Differences between groups in the change from baseline are all shown as means with 95% CIs.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; CRP, C-reactive protein; TNFα, tumor necrosis factor α; IL6, interleukin 6; IL10, interleukin 10; ICAM1, intercellular adhesion molecule 1; CD14, cluster of differentiation 14; MCP1, monocyte chemoattractant protein 1; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; MVPA, moderate-to-vigorous physical activity; CPM, counts per minute; PSS, perceived stress scale; TFEQ, three factor eating questionnaire.
[a] Observed (n = 182), estimated (n = 200).
[b] Observed data (n = 181), estimated (n = 200).
[c] Observed data (n = 180), estimated (n = 198).
[d] Observed data (n = 179), estimated (n = 200).
[e] Observed data (n = 177), estimated (n = 200).
[f] $p < 0.01$ significant change from baseline.
[g] $p < 0.05$ significant change from baseline.

NUGENOB), and retrospectively classified participants into three distinct metabotypes (normoglycemia, prediabetes, or diabetes) based on baseline markers of glucose metabolism. This analysis demonstrated that individuals with normoglycemia at baseline lost most weight on a low-fat high-carbohydrate diet, whereas those with prediabetes at baseline benefited more from a low-glycemic index diet rich in fiber and whole grains [32,33]. In our study, 49 individuals were classified in the carbohydrate cluster, reflecting compromised glucose metabolism at baseline. The personalized diet for this cluster was particularly rich in fiber (51 g/d), yet we found no significant differences between groups in body weight and fat mass loss, or any other health outcome. Nevertheless, we cannot exclude the possibility that this was due to the control diet for this cluster being also high in fiber (33 g/d).

4.2. Cardiometabolic risk factors and inflammatory markers

Findings from the population-based Rotterdam study indicate that a diet rich in plant-based foods, but not necessarily a vegetarian or vegan pattern, is associated with reduced adiposity and improved insulin sensitivity, even after adjusting for BMI [34,35]. Like previous intervention trials [36–38], our results are in line with these observations. The personalized and control diets in our study were both mostly plant-based and both had beneficial effects on a variety of cardiometabolic risk factors, likely concomitant to the modest but significant weight loss. Nevertheless, with the exception of leptin concentration that decreased with fat mass loss, as expected [26], we did not observe any significant changes in other pro-inflammatory markers after a 3.2% weight loss. This is in agreement with Forsythe et al. [39], who concluded that at least 10% weight loss is required to bring about robust improvements in obesity-related inflammatory markers [39]. Likewise, Magkos et al. [26] reported that a diet-induced 5% weight loss did not significantly improve circulating levels of CRP, TNFα, IL6, or MCP1 [26]. These data collectively indicate that weight loss is the predominant factor for diet-induced improvements in cardiometabolic risk factors and inflammatory markers, with the former requiring less weight loss to improve than the latter. Our results further suggest that personalizing the diet beyond a generally healthy pattern offers no further advantage.

4.3. Behaviour change

Contrary to the absence of sufficient evidence on hard endpoints, such as body weight and fat mass and cardiometabolic risk factors, it is well established that personalized health advice is more engaging and may provide greater motivation for changing behavior, improving dietary patterns, and increasing physical activity than conventional, generic, one-fits-all advice [40–43]. For example, the Food4Me trial demonstrated that the group receiving personalized advice adopted a significantly healthier eating pattern compared to the control group, regardless of whether the personalization was based on phenotypic or genotypic data [31]. In our study, we delivered healthy plant-based meals to all participants' doorstep, free-of-charge, and this invariably led to a shift towards healthier eating patterns. This could help explain why we did not observe any differences in eating behavior outcomes between our two groups; both significantly reduced their intake of saturated fat and added sugar, and increased intake of fiber. Furthermore, TFEQ-restraint increased while TFEQ-disinhibition/hunger decreased in both groups, indicating positive attitude toward dieting behaviors, as observed previously [44–46]. Although subjects randomized to the personalized group seemed to increase their physical activity and those randomized to the control group seemed to decrease their physical activity, these differences did not reach significance and were overall minor. Reasons for this may include the naturally large interindividual variability in physical activity levels, the relatively small sample size, or the fact that our trial was carried out during COVID-19 lockdown restrictions in Denmark which limited opportunities for physical activity [47].

4.4. Strengths and limitations

A key strength of our study is the double-blinded randomized design; both intervention arms received similarly intensive focus on diet quality and both received about 60% of their weekly meals free-of-charge, supported with dietary and behavioral messages to facilitate adherence. Moreover, retention rates were satisfactory and similar between groups (personalized: 78%; control: 86%), and our intention-to-treat analysis utilized all available data. Still, interpretation of our results should be made with caution given some limitations. The generalizability is limited by the small overall number of participants, which was likely not adequate to reach statistical significance in some of the secondary outcomes (e.g. physical activity change between groups). Importantly, both study groups received meals consisting of healthy vegetarian foods with similar macronutrient composition, together with health-promoting behavioral advice, whether personalized or not. In other words, the control diet was likely healthier than the habitual diet consumed by our participants. This could be overcome by adding an additional, inactive arm as a reference group (i.e. no meals or behavioral advice). Also, for reasons related to study cost, we could provide only 12 out of the 21 weekly meals, corresponding to ~60% of total food intake. Lastly, while the duration of our intervention (10 weeks) was adequate for improvements in weight, body composition, and some of the cardiometabolic biomarkers to manifest after both diets, a longer duration might have provided more insight into the potential of diet personalization to establish longer-lasting changes.

5. Conclusion

Contrary to our hypothesis, a personalized dietary plan informed by a combination of omics technologies did not yield greater benefits on body weight homeostasis, body composition, and various health outcomes in individuals with overweight and obesity, beyond those obtained by a one-diet-fits-all approach. Therefore, it remains unknown whether the personalization of lifestyle interventions is more effective than generic dietary advice in changing health-related behaviors to ultimately affect health outcomes and mitigate nutrition-related chronic diseases. Future studies should test this premise under calorie restricted regimens as well, and include precise measurements not only of energy intake but also of energy expenditure, physical activity, and weight loss-induced metabolic adaptations. For the time being, however, evidence to translate personalized nutrition approaches into clinical practice is insufficient.

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Author Contributions

Conceptualization: BG, ANC and JMDB; Study design: MAA, KP, MFH, FM, SMOG, BG, ANC, JMDB; Statistical analysis: MAA; cluster allocation analysis: FS, MP, SG, AP, XE, JMAH, MG, DS, MGC, MARG;

Investigation: KP, MAA, MFH, FM; Data curation: MAA, KP, XE, JMAH, MG, DS; Writing—original draft: MAA, FM; Writing—review & editing: KP and MFH; Supervision: MFH and FM; Project administration: BG, MFH, FM; Funding acquisition: BG and JMDB. All authors have critically reviewed, read and approved the final version of the manuscript.

Data Availability

The authors are committed to responsible sharing of the data that support the findings of this study. This includes anonymized individual participant data and other materials such as study protocols. Requests from researchers who provide a methodologically sound proposal should be addressed to the corresponding author.

Conflict of interest

SMOG is an employee of Simple Feast (Copenhagen, Denmark) that provided food as study material. The remaining authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.06.032.

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